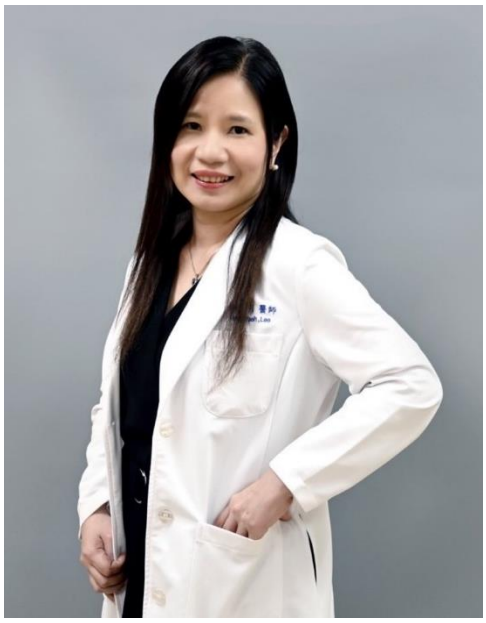

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腎臟多組學遺傳評分卡揭示編碼與調控變異的匯聚現象

前言

全球有超過 8 億人罹患腎臟疾病，每年約有近百萬人因腎衰竭死亡。腎功能具有高度遺傳性，主要受常見的遺傳變異影響。全基因組關聯研究（GWAS）已揭示許多與疾病相關的變異，但其中超過 90%位於非編碼區域，這使得我們難以明確找出其所影響的基因與調控機制，這個挑戰被稱為「變異至基因(variant-to-gene)」或「變異至功能（variant-to-function）」問題。

研究動機

過去十年來，研究人員開發了多種工具，試圖將遺傳變異與疾病發展連結起來，例如透過基因表現數量性狀位點（eQTL）、染色質可及性（acQTL）與 DNA 甲基化（meQTL）等方式。對等位基因特異性表現的分析，亦有助於更精確地定位具功能性的調控變異。此外，單細胞多模態技術也讓研究得以精細到單一細胞層級。本研究的目的是建構腎絲球過濾率（GFR）的遺傳圖譜，並結合多種組學資料與分析工具，找出與腎功能調控相關的變異、基因與細胞類型。

研究結果

我們針對 220 萬人進行了跨族群的 GWAS，利用血清肌酸酐估算腎絲球過濾率（eGFRcrea）作為腎功能指標。分析結果共鑑定出 1026 個獨立遺傳位點，其中有 97 個為全新發現。比較歐洲、東亞與非洲族群的資料，我們發現新信號在歐洲族群中較弱，強調了族群多樣性對於遺傳研究的重要性。

此外，我們分析了超過 700 份腎臟樣本與 237,000 個單細胞中的等位基因特異性表現與調控機制。透過我們開發的統計方法 Open4Gene，鑑定出 1351 個位於開放染色質區域的遺傳變異所對應的靶基因。

我們也提出了「腎病遺傳評分卡（Kidney Disease Genetic Scorecard）」的概念，整合 32 種資料來源，幫助識別與腎病相關的致病變異與基因。此評分卡共優先挑選出 24,437 個調控變異，對應到 1060 個基因。我們也觀察到編碼變異與調控變異在某些關鍵基因上呈現匯聚現象，共發現 1363 個編碼變異影響 782 個基因，其中 601 個基因同時也受到調控變異影響。有 124 個基因更是現有 FDA 核准藥物的標的，提供了藥物再定位與新療法開發的潛力。

結論

本研究提供了一份針對腎功能的遺傳藍圖，為基於遺傳的疾病預測與藥物開發奠定基礎。我們以大規模多組學資料，深入解析人類腎功能的遺傳結構，並強調編碼與調控變異在致病基因上的交集，進一步提出「腎病遺傳評分卡」概念，有助於腎病的診斷與治療策略發展。

Kidney multiome-based genetic scorecard reveals convergent coding and regulatory variants

INTRODUCTION

More than 800 million people worldwide suffer from kidney disease, with nearly 1 million dying annually from renal failure. Kidney function is highly heritable, predominantly influenced by common genetic variants. Genome-wide association studies (GWASs) map associations between these variants and disease, yet more than 90% of GWAS-identified variants reside in noncoding genome regions. This presents notable challenges in pinpointing their target genes and regulatory functions, a dilemma known as the “variant-to-gene” or “variant-to-function” problem.

RATIONALE

In the past decade, various tools have been developed to connect genetic variants to disease development. These include mapping the association of variants with quantitative traits, such as gene expression (eQTL; QTL, quantitative trait loci), chromatin

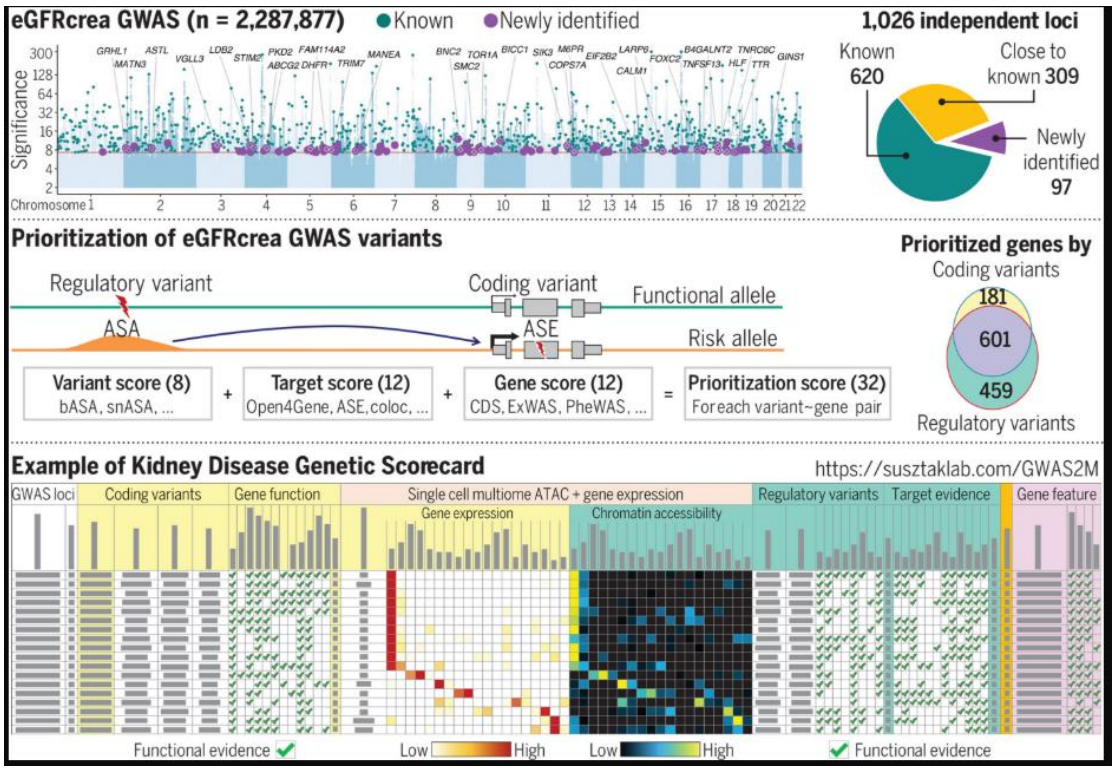
accessibility (acQTL), and DNA methylation (meQTL). Allele-specific analysis offers valuable insights for fine-mapping these elusive causal regulatory variants. Single-cell multimodal methodologies have further enabled analysis at the single-cell level. This study aimed to define the genetic architecture of glomerular filtration rate (GFR) and use complementary omics datasets and tools to nominate regulatory variants, genes, and cell types involved in kidney function regulation.

RESULTS

We conducted a multiancestry GWAS for kidney function, measured by the estimated GFR based on serum creatinine (eGFRcrea), involving 2.2 million individuals. Our analysis identified 1026 (97 previously unknown) independent loci. By mapping kidney function–associated common DNA variants across European-, East Asian–, and African-ancestry populations, we observed an attenuation of newly identified signals in European populations and highlighted the value of population diversity for further discoveries.

Additionally, we analyzed genotype effects on allele-specific gene expression and regulatory circuitries in more than 700 kidneys and 237,000 cells. We developed a statistical approach named Open4Gene, which identified 1351 target genes of genetic variants located within open chromatin regions.

Furthermore, we introduced the “Kidney Disease Genetic Scorecard” concept, which integrates 32 types of data to support genetic information and nominate causal genetic variants and genes for kidney disease. The Kidney Disease Genetic Scorecard prioritized 24,437 regulatory variants targeting 1060 genes. We also observed convergence of coding and regulatory variations in specific genes, identifying 1363 coding variants disrupting 782 genes, with 601 genes also targeted by regulatory variants. Notably, 124 genes were identified as amenable to targeting by FDA-approved drugs, presenting opportunities for drug repurposing and therapeutic development.



CONCLUSION

We provide a genetic blueprint for kidney function, enabling genetics-based prognostication and drug discovery. This study presents a large-scale analysis of the genetic architecture of human kidney function, utilizing various omics datasets to offer biological insights. Emphasizing the convergence of coding and regulatory variants on key disease genes, we introduce the concept of a Kidney Disease Genetic Scorecard for disease diagnostics and therapeutic development.